# .NT COOPERATION TREAT.

#### From the INTERNATIONAL BUREAU

### PCT

### **NOTIFICATION OF ELECTION**

(PCT Rule 61.2)

Commissioner **US Department of Commerce United States Patent and Trademark** 

Office, PCT

2011 South Clark Place Room

CP2/5C24

Arlington, VA 22202

Date of mailing (day/month/year) 14 December 2000 (14.12.00)	ETATS-UNIS D'AMERIQUE in its capacity as elected Office
International application No.	Applicant's or agent's file reference
PCT/EP00/03407	FC 859
International filing date (day/month/year)	Priority date (day/month/year)
14 April 2000 (14.04.00)	18 May 1999 (18.05.99)
Applicant	
DI SALLE, Enrico et al	

1.	The designated Office is hereby notified of its election made:
	X in the demand filed with the International Preliminary Examining Authority on:
	23 November 2000 (23.11.00)
	in a notice effecting later election filed with the International Bureau on:
2.	The election X was
	was not
	made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).
	•

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland

Authorized officer

**Nestor Santesso** 

Telephone No.: (41-22) 338.83.38

### PCT

### NOTIFICATION CONCERNING SUBMISSION OR TRANSMITTAL OF PRIORITY DOCUMENT

(PCT Administrative Instructions, Section 411)

From the	INTERNATIO	NAL BUREAU
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To:

PHARMACIA & UPJOHN S.P.A Viale Pasteur 1 o I-20014 Nerviano ITALIE

Date of mailing (day/month/year) 23 May 2000 (23.05.00)	
Applicant's or agent's file reference FC 859	IMPORTANT NOTIFICATION
International application No. PCT/EP00/03407	International filing date (day/month/year) 14 April 2000 (14.04.00)
International publication date (day/month/year) Not yet published	Priority date (day/month/year) 18 May 1999 (18.05.99)
Applicant  PHARMACIA & LIP IOHN S. P. A. et al.	

- 1. The applicant is hereby notified of the date of receipt (except where the letters "NR" appear in the right-hand column) by the International Bureau of the priority document(s) relating to the earlier application(s) indicated below. Unless otherwise indicated by an asterisk appearing next to a date of receipt, or by the letters "NR", in the right-hand column, the priority document concerned was submitted or transmitted to the International Bureau in compliance with Rule 17.1(a) or (b).
- 2. This updates and replaces any previously issued notification concerning submission or transmittal of priority documents.
- 3. An asterisk(\*) appearing next to a date of receipt, in the right-hand column, denotes a priority document submitted or transmitted to the International Bureau but not in compliance with Rule 17.1(a) or (b). In such a case, the attention of the applicant is directed to Rule 17.1(c) which provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.
- 4. The letters "NR" appearing in the right-hand column denote a priority document which was not received by the International Bureau or which the applicant did not request the receiving Office to prepare and transmit to the International Bureau, as provided by Rule 17.1(a) or (b), respectively. In such a case, the attention of the applicant is directed to Rule 17.1(c) which provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.

Priority date Priority application No. Country or regional Office or PCT receiving Office of priority document

18 May 1999 (18.05.99) 9911582.6 GB 04 May 2000 (04.05.00)

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland

Authorized officer

Aino Meteolfe

Telephone No. (41-22) 338.83.38

Facsimile No. (41-22) 740.14.35

# INT ATIONAL SEARCH REPORT

PCT/FP 00/03407

,	_	P	CI/EP 00/0340/
A. CLASS	IFICATION OF SUBJECT MATTER A61K45/06 A61P35/00		
	o International Patent Classification (IPC) or to both national	classification and IPC	
	SEARCHED  ocumentation searched (classification system followed by cla	ssification symbols)	
IPC 7	A61K	ioonioanon oyniboo,	
Documenta	tion searched other than minimum documentation to the exte	nt that such documents are included	in the fields searched
Electronic d	ata base consulted during the international search (name of	data base and, where practical, sea	arch terms used)
EPO-In	ternal, PAJ, WPI Data, BIOSIS, C	CHEM ABS Data, EMBA	SE
C. DOCUME	ENTS CONSIDERED TO BE RELEVANT		
Category °	Citation of document, with indication, where appropriate, of	the relevant passages	Relevant to claim No.
X	J.L. GREM E.A.: "A phase II combination chemotherapy plus aminoglutethimide in women wi or recurrent breast carcinoma AMERICAN JOURNAL OF CLINICAL vol. 11, no. 5, 1988, pages 5 XP000929348 page 528	th metastatic " ONCOLOGY,	1-4, 10-15,21
Furthe	er documents are listed in the continuation of box C.	Patent family memb	pers are listed in annex.
" documen consider " earlier do filling dat " document which is citation of document document	t which may throw doubts on priority claim(s) or cited to establish the publication date of another or other special reason (as specified) t referring to an oral disclosure, use, exhibition or	or priority date and not incited to understand the invention  "X" document of particular recannot be considered in inventive step  "Y" document of particular recannot be considered to document is combined of ments, such combination in the art.  "&" document member of the	
te of the ac	tual completion of the international search	Date of mailing of the int	ernational search report
25	July 2000	08/08/2000	
me and mai	iling address of the ISA  European Patent Office, P.B. 5818 Patentlaan 2  NL - 2280 HV Rijswijk  Tel. (+31-70) 340-2040, Tx. 31 651 epo ni,	Authorized officer Peeters, J	



Ir. lational Application No PCT/EP 00/03407

A. CLASSI IPC 7	FICATION OF SUBJECT MATTER A61K45/06 A61P35/00		
According to	o International Patent Classification (IPC) or to both national classi	fication and IPC	
B. FIELDS	SEARCHED		
Minimum do IPC 7	cumentation searched (classification system followed by classific A61K	ation symbols)	
Documentat	ion searched other than minimum documentation to the extent the	t such documents are included in the fid	elds searched
Electronic d	ata base consulted during the international search (name of data	pase and, where practical, search terms	s used)
EPO-In	ternal, PAJ, WPI Data, BIOSIS, CHE	M ABS Data, EMBASE	
	ENTS CONSIDERED TO BE RELEVANT		
Category °	Citation of document, with indication, where appropriate, of the	relevant passages	Relevant to claim No.
X	J.L. GREM E.A.: "A phase II every combination chemotherapy plus aminoglutethimide in women with or recurrent breast carcinoma" AMERICAN JOURNAL OF CLINICAL ON vol. 11, no. 5, 1988, pages 528-XP000929348 page 528	metastatic	1-4, 10-15,21
Furth	ner documents are listed in the continuation of box C.	Patent family members are	listed in annex.
° Special ca	tegories of cited documents:	"T" later document sublished effects	a international filing data
"A" docume	ent defining the general state of the art which is not	"T" later document published after the or priority date and not in conflict	t with the application but
consid "E" earlier o	ered to be of particular relevance tocument but published on or after the international	cited to understand the principle invention "X" document of particular relevance;	
filing d "L" docume which	ate nt which may throw doubts on priority claim(s) or is cited to establish the publication date of another	cannot be considered novel or c involve an inventive step when t	annot be considered to he document is taken alone
citation	n or other special reason (as specified) ont referring to an oral disclosure, use, exhibition or	"Y" document of particular relevance; cannot be considered to involve document is combined with one	an inventive step when the
other r	neans ont published prior to the international filing date but	ments, such combination being of in the art.	obvious to a person skilled
	an the priority date claimed actual completion of the international search	"&" document member of the same p  Date of mailing of the internation	
	5 July 2000	08/08/2000	
Name and n	nailing address of the ISA  European Patent Office, P.B. 5818 Patentlaan 2  NL – 2280 HV Rijswijk  Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,	Authorized officer	
	Fax: (+31-70) 340-3016	Peeters, J	

Pharmacia & Upjohn S.p.A. BREVETTI





30 NOV 2000

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PCT

### From the INTERNATIONAL BUREAU

To:

PHARMACIA & UPJOHN S.P.A Viale Pasteur 1 o I-20014 Nerviano ITALIE

# NOTICE INFORMING THE APPLICANT OF THE COMMUNICATION OF THE INTERNATIONAL APPLICATION TO THE DESIGNATED OFFICES

(PCT Rule 47.1(c), first sentence)

Date of mailing (day/month/year)
23 November 2000 (23.11.00)

Applicant's or agent's file reference

FC 859

**IMPORTANT NOTICE** 

International application No. PCT/EP00/03407

International filing date (day/month/year) 14 April 2000 (14.04.00) Priority date (day/month/year) 18 May 1999 (18.05.99)

Applicant

PHARMACIA & UPJOHN S.P.A. et al

Notice is hereby given that the International Bureau has communicated, as provided in Article 20, the international application
to the following designated Offices on the date indicated above as the date of mailing of this Notice:
AU,KP,KR,US

In accordance with Rule 47.1(c), third sentence, those Offices will accept the present Notice as conclusive evidence that the communication of the international application has duly taken place on the date of mailing indicated above and no copy of the international application is required to be furnished by the applicant to the designated Office(s).

2. The following designated Offices have waived the requirement for such a communication at this time:

AE,AL,AM,AP,AT,AZ,BA,BB,BG,BR,BY,CA,CH,CN,CR,CU,CZ,DE,DK,DM,EA,EE,EP,ES,FI,GB,GD,GE,GH,GM,HR,HU,ID,IL,IN,IS,JP,KE,KG,KZ,LC,LK,LR,LS,LT,LU,LV,MA,MD,MG,MK,MN,MW,MX,NO,NZ,OA,PL,PT,RO,RU,SD,SE,SG,SI,SK,SL,TJ,TM,TR,TT,TZ,UA,UG,UZ,VN,YU,ZA,ZW The communication will be made to those Offices only upon their request. Furthermore, those Offices do not require the applicant to furnish a copy of the international application (Rule 49.1(a-bis)).

 Enclosed with this Notice is a copy of the international application as published by the International Bureau on 23 November 2000 (23.11.00) under No. WO 00/69467

#### REMINDER REGARDING CHAPTER II (Article 31(2)(a) and Rule 54.2)

If the applicant wishes to postpone entry into the national phase until 30 months (or later in some Offices) from the priority date, a demand for international preliminary examination must be filed with the competent International Preliminary Examining Authority before the expiration of 19 months from the priority date.

It is the applicant's sole responsibility to monitor the 19-month time limit.

Note that only an applicant who is a national or resident of a PCT Contracting State which is bound by Chapter II has the right to file a demand for international preliminary examination.

#### REMINDER REGARDING ENTRY INTO THE NATIONAL PHASE (Article 22 or 39(1))

If the applicant wishes to proceed with the international application in the **national phase**, he must, within 20 months or 30 months, or later in some Offices, perform the acts referred to therein before each designated or elected Office.

For further important information on the time limits and acts to be performed for entering the national phase, see the Annex to Form PCT/IB/301 (Notification of Receipt of Record Copy) and Volume II of the PCT Applicant's Guide.

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland

Authorized officer

J. Zahra

Facsimile No. (41-22) 740.14.35

Telephone No. (41-22) 338.83.38

# **PCT**

# INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference FC 859	rit's file reference  FOR FURTHER   see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.					
International application No.	International filing date (day/month/year) (Earliest) Priority Date (day/month/year)					
PCT/EP 00/03407	. 14/04/2000	18/05/1999				
Applicant						
PHARMACIA & UPJOHN S.P.A.						
This International Search Report has beer according to Article 18. A copy is being tra	n prepared by this International Searching Auth Insmitted to the International Bureau.	ority and is transmitted to the applicant				
This International Search Report consists  X It is also accompanied by	of a total of sheets. a copy of each prior art document cited in this	report.				
Basis of the report						
	nternational search was carried out on the bas ss otherwise indicated under this item.	is of the international application in the				
the international search was Authority (Rule 23.1(b)).	as carried out on the basis of a translation of th	e international application furnished to this				
<ul> <li>b. With regard to any nucleotide and was carried out on the basis of the</li> </ul>		ernational application, the international search				
	nal application in written form.					
filed together with the inter	national application in computer readable form					
furnished subsequently to	this Authority in written form.					
	this Authority in computer readble form.					
the statement that the subs international application as	sequently furnished written sequence listing do filed has been furnished.	es not go beyond the disclosure in the				
the statement that the infor furnished	mation recorded in computer readable form is	identical to the written sequence listing has been				
2. Certain claims were found	d unsearchable (See Box I).					
3. Unity of invention is lacki	ng (see Box II).					
4. With regard to the title,						
X the text is approved as sub	mitted by the applicant.					
the text has been established	ed by this Authority to read as follows:					
5. With regard to the abstract,						
the text is approved as sub- the text has been established within one month from the co	mitted by the applicant. ed, according to Rule 38.2(b), by this Authority late of mailing of this international search repo	as it appears in Box III. The applicant may, rt, submit comments to this Authority.				
6. The figure of the <b>drawings</b> to be publish	hed with the abstract is Figure No.					
as suggested by the applica		None of the figures.				
because the applicant failed						
because this figure better ch	naracterizes the invention.					

# INTERNATIONAL SEARCH REPORT

Internal Application No PCT/EP 00/03407

A. CLASS IPC 7	A61K45/06 A61P35/00		
According	to International Patent Classification (IPC) or to both national c	elassification and IPC	
B. FIELDS	SEARCHED		
Minimum d IPC 7	ocumentation searched (classification system followed by class $A61K$	ssification symbols)	
Documenta	tion searched other than minimum documentation to the exter	nt that such documents are included in the fields s	earched
Electronic o	data base consulted during the international search (name of c	data base and, where practical, search terms used	1)
EPO-In	ternal, PAJ, WPI Data, BIOSIS, C	HEM ABS Data, EMBASE	
C. DOCUM	ENTS CONSIDERED TO BE RELEVANT		
Category °	Citation of document, with indication, where appropriate, of	the relevant passages	Relevant to claim No.
X	J.L. GREM E.A.: "A phase II combination chemotherapy plus aminoglutethimide in women without recurrent breast carcinoma AMERICAN JOURNAL OF CLINICAL vol. 11, no. 5, 1988, pages 52 XP000929348 page 528	th metastatic " ONCOLOGY,	1-4, 10-15,21
Furth	er documents are listed in the continuation of box C.	Patent family members are listed i	n annex.
° Special cat	egories of cited documents :	"T" later decument published offer the "	national filing data
consider de filing da "L" documer which is citation "O" documer other m	nt which may throw doubts on priority claim(s) or s cited to establish the publication date of another or other special reason (as specified) nt referring to an oral disclosure, use, exhibition or	"T" later document published after the inter or priority date and not in conflict with the cited to understand the principle or the invention  "X" document of particular relevance; the clum cannot be considered novel or cannot be involve an inventive step when the document of particular relevance; the clum cannot be considered to involve an inventive step when the document of particular relevance; the clum cannot be considered to involve an involve an involve an involve an involve and comment is combined with one or more ments, such combination being obvious in the art.  "&" document member of the same patent fater."	he application but ory underlying the aimed invention be considered to ument is taken alone aimed invention entive step when the e other such docu— s to a person skilled
Date of the a	ctual completion of the international search	Date of mailing of the international sear	ch report
25	July 2000	08/08/2000	
Name and ma	ailing address of the ISA  European Patent Office, P.B. 5818 Patentlaan 2  NL - 2280 HV Rijswijk  Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Authorized officer  Peeters, J	



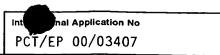
PCT

## INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

FC 859 ACTION	ACTION (Form PCT/ISA/220) as well as, where applicable, item 5 below.					
International application No. International filing date (day/month/year) (Earliest) Priority Date (day/mo	onth/year)					
PCT/EP 00/03407 14/04/2000 18/05/1999	•					
Applicant						
DHADMACTA O HD TOHAL C. D. A.						
PHARMACIA & UPJOHN S.P.A.						
This International Search Report has been prepared by this International Searching Authority and is transmitted to the ap						
according to Article 18. A copy is being transmitted to the International Bureau.	plicant					
This International Search Report consists of a total of2 sheets.						
This International Search Report consists of a total of sheets.  X It is also accompanied by a copy of each prior art document cited in this report.						
Basis of the report     a. With regard to the language, the international search was carried out on the basis of the international application.	in the					
language in which it was filed, unless otherwise indicated under this item.	III GIE					
the international search was carried out on the basis of a translation of the international application furnish Authority (Rule 23.1(b)).	ned to this					
<ul> <li>With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international application and the sequence listing:</li> </ul>	ational search					
contained in the international application in written form.						
filed together with the international application in computer readable form.						
furnished subsequently to this Authority in written form.						
furnished subsequently to this Authority in computer readble form.						
the statement that the subsequently furnished written sequence listing does not go beyond the disclosure international application as filed has been furnished.	in the					
the statement that the information recorded in computer readable form is identical to the written sequence furnished	listing has been					
Certain claims were found unsearchable (See Box I).						
3. Unity of invention is lacking (see Box II).						
4. With regard to the title,  X the text is approved as submitted by the applicant.						
the text has been established by this Authority to read as follows:						
5. With regard to the abstract,						
X the text is approved as submitted by the applicant.						
the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The approximation one month from the date of mailing of this international search report, submit comments to this Authority as it appears in Box III.	olicant may,					
6. The figure of the <b>drawings</b> to be published with the abstract is Figure No.	ionty.					
as suggested by the applicant. None of the	ne figures.					
because the applicant failed to suggest a figure.						
because this figure better characterizes the invention.						





A. CLASS IPC 7	FICATION OF SUBJECT MATTER A61K45/06 A61P35/00		
According t	o International Patent Classification (IPC) or to both national classi	ification and IPC	
B. FIELDS	SEARCHED		
	ocumentation searched (classification system followed by classific	ation symbols)	
IPC 7	A61K		
Documenta	tion searched other than minimum documentation to the extent the	at such documents are included in the fields so	earched
Electronic o	ata base consulted during the international search (name of data	hase and where practical search terms used	<u> </u>
	ternal, PAJ, WPI Data, BIOSIS, CHE	•	'
	ENTS CONSIDERED TO BE RELEVANT		
Category °	Citation of document, with indication, where appropriate, of the	relevant passages	Relevant to claim No.
X	J.L. GREM E.A.: "A phase II every combination chemotherapy plus aminoglutethimide in women with or recurrent breast carcinoma" AMERICAN JOURNAL OF CLINICAL ON vol. 11, no. 5, 1988, pages 528-XP000929348 page 528	metastatic	1-4, 10-15,21
Furti	ner documents are listed in the continuation of box C.	Patent family members are listed	in annex.
° Special ca	tegories of cited documents :	"T" later decument published after the inte	mational filing data
"A" docume	nt defining the general state of the art which is not	"T" later document published after the inte or priority date and not in conflict with	the application but
consid	ered to be of particular relevance	cited to understand the principle or the invention	eory underlying the
	ocument but published on or after the international	"X" document of particular relevance; the c	
filing d	ate nt which may throw doubts on priority claim(s) or	cannot be considered novel or cannot involve an inventive step when the do	be considered to
which	s cited to establish the publication date of another	"Y" document of particular relevance; the c	
	n or other special reason (as specified) ent referring to an oral disclosure, use, exhibition or	cannot be considered to involve an involve an involve an involve document is combined with one or mo	ventive step when the
other r	neans	ments, such combination being obviou	
	nt published prior to the international filing date but an the priority date claimed	in the art.  "&" document member of the same patent	amily
	actual completion of the international search	Date of mailing of the international sea	
2!	5 July 2000	08/08/2000	
Name and n	nailing address of the ISA	Authorized officer	
	European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Peeters, J	



# **PCT**

## INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

C A - C	10.000	months file veterance					
	Applicant's or agent's file reference  FC 859  See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA)			PEA/416)			
		P. 41 NI				· · ·	
PCT/EF	-	plication No.	International filing date	е (аау/тони	vyear)	Priority date (day/month/year) 18/05/1999	
		<u></u>	national classification and	IBC		10/03/1999	
A61K45		tent classification (IFC) of	Hational classification and	iPG			
		····			-		
Applicant							
PHARM	IACIA	A & UPJOHN S.P.A. e	et al.				
			mination report has bee t according to Article 36		by this Inter	national Preliminary Examinin	g Authority
2. This	REP	ORT consists of a total	of 6 sheets, including th	nis cover sh	neet.		•
	been .	amended and are the b		or sheets c	ontaining rec	, claims and/or drawings which tifications made before this Au e PCT).	
Thes	se anr	nexes consist of a total of	of 7 sheets.				•
	<b>.</b>						
3. This	report	t contains indications re	lating to the following ite	ems:			
1	×	Basis of the report					
11		Priority					
III	$\boxtimes$	Non-establishment of	opinion with regard to n	ovelty, inve	entive step a	nd industrial applicability	
IV		Lack of unity of invent	ion			,	
V	×		under Article 35(2) with ions suporting such sta		ovelty, inven	tive step or industrial applicabi	lity;
VI		Certain documents ci	ted				
VII		Certain defects in the	international application	ı			
VIII		Certain observations of	on the international appl	ication			
		$\cap$					
Date of sub	missio	on of the demand		Date of co	ompletion of th	is report	
23/11/20	00		•	01.06.200	)1		
		address of the international	al	Authorized	d officer		CO A SCHES PAIEVILLA
0))	D-80	pean Patent Office 298 Munich		Ludwig,	G	State of Sta	
<del></del>		+49 89 2399 - 0  Tx: 52365 +49 89 2399 - 4465	6 epmu d	Tolophone	No +49 89 2	200 9609	AND THE CHIEF OF THE FELL AND T

Telephone No. +49 89 2399 8698

International application No. PCT/EP00/03407

I. Bas	is of	the	re	port
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	ar	the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17)): Description, pages:						
	1-	12	as originally filed	,				
	CI	aims, No.:						
	1-2	23	as received on	21/05/2001	with letter of	16/05/2001		
	Dr	awings, sheets:						
	1/1	I	as originally filed					
		,						
2.			uage, all the elements marked nternational application was file					
	The	ese elements were a	vailable or furnished to this Au	thority in the fo	ollowing language:	, which is:		
			ranslation furnished for the pur	•	,	under Rule 23.1(b)).		
		the language of pu	blication of the international ap	plication (unde	er Rule 48.3(b)).			
		the language of a t 55.2 and/or 55.3).	ranslation furnished for the pur	poses of interr	national preliminary e	examination (under Rule		
3.			leotide and/or amino acid sec v examination was carried out o	•				
		contained in the int	ernational application in written	form.				
		filed together with t	he international application in c	omputer reada	able form.			
		furnished subsequently to this Authority in written form.						
		furnished subseque	ently to this Authority in comput	er readable fo	rm.			
			the subsequently furnished wri plication as filed has been furni		listing does not go b	peyond the disclosure in		
		The statement that listing has been furn	the information recorded in connished.	nputer readab	le form is identical to	the written sequence		
	The	amendments have i	resulted in the cancellation of:					
		the description,	pages:					
		the claims,	Nos.:					
		• ,						

1. With regard to the elements of the international application (Replacement sheets which have been furnished to

International application No. PCT/EP00/03407

		l the drawings,	sheets:		
5	5. 🗆	This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):			
		(Any replacement st report.)	eet containing such amendments must be referred to under item 1 and annexed to this		
6	. <b>A</b> c	dditional observations, i	inecessary:		
11	I. No	on-establishment of o	pinion with regard to novelty, inventive step and industrial applicability		
1	ob	vious), or to be industri	e claimed invention appears to be novel, to involve an inventive step (to be non- ally applicable have not been examined in respect of:		
		the entire internation	application.		
	×	claims Nos. 6, 18-19.			
be	ecau	se:			
			application, or the said claims Nos. relate to the following subject matter which does tional preliminary examination ( <i>specify</i> ):		
			s or drawings ( <i>indicate particular elements below</i> ) or said claims Nos. are so unclear inion could be formed ( <i>specify</i> ):		
	×	the claims, or said cla opinion could be form	ims Nos. 6, 18 are so inadequately supported by the description that no meaningful		
		no international searc	report has been established for the said claims Nos		
2.	and		preliminary examination cannot be carried out due to the failure of the nucleotide se listing to comply with the standard provided for in Annex C of the Administrative		
			ot been furnished or does not comply with the standard.		
		the computer readable	form has not been furnished or does not comply with the standard.		
	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement				
		ement			
		•			
	NOV	elty (N)	Yes: Claims 1-5, 7-17, 20-23		

International application No. PCT/EP00/03407

No:

Claims

Inventive step (IS)

Yes:

Claims 7

No: CI

Claims 1-5, 8-17, 20-23

Industrial applicability (IA)

Yes:

. -, - .., -- --

Claims 1-5, 7-12 (13-17, 20-23 - cf. separate sheets)

No: Claims

2. Citations and explanations see separate sheet

D1: J.L. GREM E.A.: 'A phase II evaluation of combination chemotherapy plus aminoglutethimide in women with metastatic or recurrent breast carcinoma' AMERICAN JOURNAL OF CLINICAL ONCOLOGY, vol. 11, no. 5, 1988,

pages 528-528-534, XP000929348

### Item V:

- 1. The combined use of the antineoplastic combination scheme of cyclophosphamide, doxorubine (=adriamycin), and 5-fluorouracil (CAF) he aromatase inhibitor aminoglutheimide for use in breast cancer therapy is disclosed in document D1, a study carried out in humans.
- 2. The use of combination therapy is a well known approach for cancer treatment.

For combinations of the aromatase inhibitor exemestane with the antineoplastic agents epirubicine (an anthracycline) and docetaxel (a taxane), respectively, a synergistic (superadditive) effect has been shown by the applicant in experiments with test animals (rats bearing DMBA-induced mammary tumours).

Except for the class of anthracyclines and taxanes there appears to be no support in the description for the presence of a synergistic effect for rest of the antineoplastic agents, i.e. vinca alkaloids, alkylating agents, antimetabolites, and topoisomerase I inhibitors when used in combination with an aromatase inhibitor.

Claims 1-5, 8-17, and 20-23 are therefore not regarded as inventive.

- 2.1 Novelty and inventive step appear to be present for claim 7.
- 3. For the assessment of the present claims 13-17, 20-23 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the

subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

#### Item III:

- 4. Claims 6 and 18 appear to extend beyond the content of the application as filed. A basis for these claims on page 6, lines 16-17 and 21-22 as indicated by the applicant could not be found.
- 5. Claims 13-17, 20-23 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).









# (PCT Article 36 and Rule 70)

Applicant's or agent's file reference FC 859 FOR FURT			FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No.			International filing date (day/mor	nth/year) Priority date (day/month/year)	
PCT/EP	00/03	407	14/04/2000	18/05/1999	
Internation A61K45		ent Classification (IPC) or n	ational classification and IPC		
Applicant PHARM	ACIA	& UPJOHN S.P.A. et	al.		
		ational preliminary exan smitted to the applicant		red by this International Preliminary Examining Authority	
2. This	REPO	PRT consists of a total o	f 6 sheets, including this cover	sheet.	
ŀ	This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).				
Thes	e anne	exes consist of a total o	f 7 sheets.		
3. This	report	contains indications rela	ating to the following items:		
1	$\boxtimes$	Basis of the report			
H		Priority			
Ш	$\boxtimes$	Non-establishment of o	opinion with regard to novelty, ir	nventive step and industrial applicability	
IV		Lack of unity of invention	on		
V 🖾 Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicabilit citations and explanations suporting such statement			o novelty, inventive step or industrial applicability;		
VI		Certain documents cit			
VII		Certain defects in the i	nternational application		
VIII		Certain observations o	n the international application		
Date of submission of the demand		Date of	of completion of this report		
23/11/2000			01.06.2	.2001	
	examir	address of the international	al Aùthori	rized officer	
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d			Ludw	rig, G	
Fax: +49 89 2399 - 4465			Teleph	none No. +49 89 2399 8698	

International application No. PCT/EP00/03407

	I.	Basis	of the	report
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1.	With regard to the <b>elements</b> of the international application (Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17)): <b>Description</b> , pages:							
	1-1	2	as originally filed					
	Cla	Claims, No.:						
	1-2	23	as received on	21/05/2001	with letter of	16/05/2001		
	Dra	awings, sheets:						
	1/1		as originally filed					
2.		With regard to the language, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.						
	These elements were available or furnished to this Authority in the following language: , which is:							
		☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).						
3.			eleotide and/or amino acid y examination was carried					
		$\square$ contained in the international application in written form.						
		filed together with the international application in computer readable form.						
		furnished subsequently to this Authority in written form.						
		furnished subsequently to this Authority in computer readable form.						
		The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.						
		The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.						
4.	The	amendments have	resulted in the cancellation	n of:				
		the description,	pages:					
		the claims,	Nos.:			•		

International application No. PCT/EP00/03407

		the drawings, sheets:			
5.		This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):			
		(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)			
6.	Add	itional observations, if necessary:			
111	. No	establishment of opinion with regard to novelty, inventive step and industrial applicability			
1.	The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:				
		the entire international application.			
	☒	claims Nos. 6, 18-19.			
be	caus	e:			
		the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination ( <i>specify</i> ):			
		the description, claims or drawings (indicate particular elements below) or said claims Nos. are so unclear that no meaningful opinion could be formed (specify):			
	×	the claims, or said claims Nos. 6, 18 are so inadequately supported by the description that no meaningful opinion could be formed.			
		no international search report has been established for the said claims Nos			
2.	and	eaningful international preliminary examination cannot be carried out due to the failure of the nucleotide or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative uctions:			
		the written form has not been furnished or does not comply with the standard.			
		the computer readable form has not been furnished or does not comply with the standard.			
		soned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; ions and explanations supporting such statement			
1.	State	ment			
	Nov	eltv (N) Yes: Claims 1-5 7-17 20-23			

International application No. PCT/EP00/03407

No:

Claims

Inventive step (IS)

Yes:

Claims 7

No:

Claims 1-5, 8-17, 20-23

Industrial applicability (IA)

Yes:

Claims 1-5, 7-12 (13-17, 20-23 - cf. separate sheets) Claims No:

2. Citations and explanations see separate sheet

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- 1. The combined use of the antineoplastic combination scheme of cyclophosphamide, doxorubine (=adriamycin), and 5-fluorouracil (CAF) he aromatase inhibitor aminoglutheimide for use in breast cancer therapy is disclosed in document D1, a study carried out in humans.
- 2. The use of combination therapy is a well known approach for cancer treatment.

For combinations of the aromatase inhibitor exemestane with the antineoplastic agents epirubicine (an anthracycline) and docetaxel (a taxane), respectively, a synergistic (superadditive) effect has been shown by the applicant in experiments with test animals (rats bearing DMBA-induced mammary tumours).

Except for the class of anthracyclines and taxanes there appears to be no support in the description for the presence of a synergistic effect for rest of the antineoplastic agents, i.e. vinca alkaloids, alkylating agents, antimetabolites, and topoisomerase I inhibitors when used in combination with an aromatase inhibitor.

Claims 1-5, 8-17, and 20-23 are therefore not regarded as inventive.

- 2.1 Novelty and inventive step appear to be present for claim 7.
- 3. For the assessment of the present claims 13-17, 20-23 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the

medical treatment.

subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new

#### Item III:

- 4. Claims 6 and 18 appear to extend beyond the content of the application as filed. A basis for these claims on page 6, lines 16-17 and 21-22 as indicated by the applicant could not be found.
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# JC12 Rec'd PCT/PTO 1 9 NOV 2001

## Claims

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- 1. A composition for use in breast cancer therapy in humans comprising, in amounts effective to produce a superadditive antitumour effect, (a) an antineoplastic agent in a pharmaceutically acceptable carrier and/or diluent, and (b) an aromatase inhibitor in a pharmaceutically acceptable carrier and/or diluent, provided that when the antineoplastic agent is a combination consisting of cyclophosphamide, doxorubicin and 5-fluorouracyl, then the aromatase inhibitor is not aminogluthetimide.
- 2. A composition according to claim 1, wherein the antineoplastic agent is selected from an antineoplastic topoisomerase II inhibitor, an antineoplastic antimicrotubule agent, an antineoplastic alkylating agent, an antineoplastic antimetabolite, and an antineoplastic topoisomerase I inhibitor, and the aromatase inhibitor is selected from exemestane, formestane, fadrozole, vorozole, letrozole, anastrozole and YM 511.
  - 3. A composition according to claim 2. wherein the antineoplastic agent is selected from an anthracycline compound, an anthraquinone compound, a podophillotoxine compound, a taxane compound, a vinca alkaloid, an alkylating agent, an antineoplastic antimetabolite agent and an antineoplastic topoisomerase I inhibitor.
  - 4. A composition according to claim 3, wherein the anthracycline compound is selected from doxorubicin, epirubicin, idarubicin and nemorubicin; the anthraquinone compound is selected from mitoxantrone and losoxantrone; the podophillotoxine compound is selected from etoposide and teniposide; the taxane compound is selected from paclitaxel and docetaxel; the vinca alkaloid is selected from vinblastine and vinorelbine; the alkylating agent is selected from cyclophosphamide, ifosfamide, melphalan and PNU 159548; the antineoplastic antimetabolite agent is selected from 5-fluorouracil, capecitabine, gemcitabine, methotrexate and edatrexate; and the antineoplastic topoisomerase I inhibitor is selected from topotecan, irinotecan, 9-nitrocamptothecin and PNU 166148.

- 5. A composition according to claim 3, wherein such a composition comprises 1, 2 or 3 antineoplastic agents selected from epirubicin, doxorubicin, idarubicin, paclitaxel, docetaxel, 5-fluorouracil, cyclophosphamide and vinorelbine, and 1 or 2 steroidal aromatase inhibitors selected from exemestane, formestane, anastrozole, letrozole and fadrozole.
- 6. A composition according to claim 2, wherein the antineoplastic agent is selected from an anthracycline and a taxane compound and the steroidal aromatase inhibitor is exemestane.

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- 7. A composition according to claim 5, wherein the composition comprises one or two antineoplastic agents selected from epirubicin and docetaxel and the steroidal aromatase inhibitor is exemestane.
- 8. A composition, according to anyone of the preceding claims, wherein:
  - the effective antineoplastic amount of vinblastine is from about 3 mg/m<sup>2</sup> to about 10 mg/m<sup>2</sup>;
  - the effective antineoplastic amount of doxorubicin is from about 20 mg/m<sup>2</sup> to about 100 mg/m<sup>2</sup>;
  - the effective antineoplastic amount of epirubicin is from about 20 mg/m<sup>2</sup> to about 200 mg/m<sup>2</sup>;
    - the effective antineoplastic amount of idarubicin is from about 1 mg/m² to about 50 mg/m²;
    - the effective antineoplastic amount of mitoxantrone is from about 10mg/m<sup>2</sup> to about 20 mg/m<sup>2</sup>;
    - the effective antineoplastic amount of paclitaxel is from about 100 mg/m<sup>2</sup> to about 300 mg/m<sup>2</sup>;
    - the effective antineoplastic amount of docetaxel is from about 50 mg/m<sup>2</sup> to about 100 mg/m<sup>2</sup>;
- the effective antineoplastic amount of vinorelbine is from about 15 mg/m<sup>2</sup> to about 30 mg/m<sup>2</sup>;

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- the effective antineoplastic amount of cyclophosphamide is from about 100 mg/m<sup>2</sup> to about 1500 mg/m<sup>2</sup>;
- the effective antineoplastic amount of melphalan is from about 1 mg/m<sup>2</sup> to about 10 mg/m<sup>2</sup>;
- the effective antineoplastic amount of 5-fluorouracil is from about 100 mg/m<sup>2</sup> to about 1000 mg/m<sup>2</sup>;
  - the effective antineoplastic amount of capecitabine is from about 10 mg/m<sup>2</sup> to about 1000 mg/m<sup>2</sup>;
  - the effective antineoplastic amount of methotrexate is from about 10 mg/m<sup>2</sup> to about 1000 mg/m<sup>2</sup>;
  - the effective antineoplastic amount of topotecan is from about 1 mg/m<sup>2</sup> to about 5 mg/m<sup>2</sup>;
  - the effective antineoplastic amount of irinotecan is from about 50 mg/m<sup>2</sup> to about 350 mg/m<sup>2</sup>;
- and the effective amount of aromatase inhibitor is from about 0.5 to about 500 mg.
  - 9. A composition according to claim 8, wherein when administered orally, the amount of aromatase inhibitor exemestane is from about 5 to about 200 mg, fadrozole from about 0.5 to about 10 mg, letrozole from about 0.5 to about 10 mg, and anastrozole from about 0.5 to about 10 mg.
  - 10. A composition according to claim 8, wherein when administered parenterally, the amount of aromatase inhibitor exemestane is from about 50 to about 500 mg, and formestane is from about 250 to about 500 mg.
  - 11. A product containing an antineoplastic agent and an aromatase inhibitor, in amounts effective to produce a superadditive antitumor effect, for separate, simultaneous or sequential administration in breast cancer therapy in humans, and wherein when the antineoplastic agent is a combination consisting of cyclophosphamide, doxorubicin and 5-fluorouracyl, then the aromatase inhibitor is not aminogluthetimide.

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- 12. Use of an antineoplastic agent in the manufacture of a pharmaceutical composition for the treatment of breast cancer in a method additionally comprising the administration of an aromatase inhibitor, in amounts effective to produce a superadditive antitumor effect, and wherein when the antineoplastic agent is a combination consisting of cyclophosphamide, doxorubicin and 5-fluorouracyl, then the aromatase inhibitor is not aminogluthetimide.
- 13. A method for treating breast cancer in humans, the method comprising administering to a human in need thereof (a) an antineoplastic agent and (b) an aromatase inhibitor, in amounts effective to produce a superadditive antitumor effect, provided that when the antineoplastic agent is a combination consisting of cyclophosphamide, doxorubicin and 5-fluorouracyl, then the aromatase inhibitor is not aminogluthetimide.
- 14. A method, according to claim 13, wherein the antineoplastic agent is selected from an antineoplastic topoisomerase II inhibitor, an antineoplastic antimicrotubule agent, an antineoplastic alkylating agent, an antineoplastic antimetabolite and an antineoplastic topoisomerase I inhibitor, and the aromatase inhibitor is selected from exemestane, formestane, fadrozole, vorozole, letrozole, anastrozole and YM 511.

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15. A method according to claim 14, wherein the antineoplastic agent is selected from an anthracycline compound, an anthraquinone compound, a podophillotoxine compound, a taxane compound, a vinca alkaloid, an alkylating agent, an antineoplastic antimetabolite agent and an antineoplastic topoisomerase I inhibitor.

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16. A method according to claim 15, wherein the anthracycline compound is selected from doxorubicin, epirubicin, idarubicin and nemorubicin; the anthraquinone compound is selected from mitoxantrone and losoxantrone; the podophillotoxine compound is selected from etoposide and teniposide; the taxane compound is selected from paclitaxel and docetaxel; the vinca alkaloid is selected from vinblastine and vinorelbine; the alkylating agent is selected from cyclophosphamide ifosfamide, melphalan and PNU 159548; the antineoplastic antimetabolite agent is selected from 5-

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fluorouracil, capecitabine, gemcitabine, methotrexate and edatrexate; and the antineoplastic topoisomerase I inhibitor is selected from topotecan, irinotecan, 9-nitrocamptothecin and PNU 166148.

- 17. A method according to claim 15, wherein 1, 2 or 3 antineoplastic agents selected from epirubicin, doxorubicin, idarubicin, paclitaxel, docetaxel, 5-fluorouracil, cyclophosphamide and vinorelbine, and 1 or 2 steroidal aromatase inhibitors selected from exemestane, formestane, anastrozole, letrozole and fadrozole are administered.
- 18. A method according to claim 14, wherein the antineoplastic agent is selected from an anthracycline compound and a taxane compound and the steroidal aromatase inhibitor is exemestane.
- 19. A method according to claim 18, wherein one or two antineoplastic agents selected from epirubicin and docetaxel and the steroidal aromatase inhibitor exemestane are administered.
  - 20. A method according to claim 16 or 17, wherein:
  - the effective antineoplastic amount of vinblastine is from about 3 mg/m<sup>2</sup> to about 10 mg/m<sup>2</sup>;
  - the effective antineoplastic amount of doxorubicin is from about 20 mg/m<sup>2</sup> to about 100 mg/m<sup>2</sup>;
  - the effective antineoplastic amount of epirubicin is from about 20 mg/m<sup>2</sup> to about 200 mg/m<sup>2</sup>;
  - the effective antineoplastic amount of idarubicin is from about 1 mg/m<sup>2</sup> to about 50 mg/m<sup>2</sup>;
    - the effective antineoplastic amount of mitoxantrone is from about 10 mg/m<sup>2</sup> to 10 about 20 mg/m<sup>2</sup>;
    - the effective antineoplastic amount of paclitaxel is from about 100 mg/m² to about 300 mg/m²;
    - the effective antineoplastic amount of docetaxel is from about 50 mg/m<sup>2</sup> to about 100 mg/m<sup>2</sup>;

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- the effective antineoplastic amount of vinorelbine is from about 15 mg/m<sup>2</sup> to about 30 mg/m<sup>2</sup>;
- the effective antineoplastic amount of cyclophosphamide is from about 100 mg/m<sup>2</sup> to about 1500 mg/m<sup>2</sup>;
- the effective antineoplastic amount of melphalan is from about 1 mg/m<sup>2</sup> to about 10 mg/m<sup>2</sup>;
- the effective antineoplastic amount of 5-fluorouracil is from about 100 mg/m<sup>2</sup> to about 1000 mg/m<sup>2</sup>;
- the effective antineoplastic amount of capecitabine is from about 10 mg/m<sup>2</sup> to about 1000 mg/m<sup>2</sup>;
- the effective antineoplastic amount of methotrexate is from about 10 mg/m<sup>2</sup> to about 1000 mg/m<sup>2</sup>;
- the effective antineoplastic amount of topotecan is from about 1 mg/m<sup>2</sup> to about 5 mg/m<sup>2</sup>;
- the effective antineoplastic amount of irinotecan is from about 50 mg/m<sup>2</sup> to about 30 350 mg/m<sup>2</sup>;

and the effective amount of aromatase inhibitor is from about 0.5 to about 500 mg.

- 21. A method according to claim 19, wherein when administered orally, the amount of aromatase inhibitor exemestane is from about 5 to about 200 mg, fadrozole from about 0.5 to about 10 mg, letrozole from about 0.5 to about 10 mg, and anastrozole from about 0.5 to about 10 mg.
- 22. A method according to claim 19, wherein when administered parenterally, the amount of aromatase inhibitor exemestane is from about 5 to about 500 mg, and formestane is from about 250 to about 500 mg.
  - 23. A method for lowering the side effects in humans caused by breast cancer therapy with an antineoplastic agent, the method comprising administering to a human in need thereof a combined preparation comprising (a) an antineoplastic agent and (b) an aromatase inhibitor, in a quantity to produce a superadditive antitumor effect, provided that when the antineoplastic agent is a combination consisting of

cyclophosphamide, doxorubicin and 5-fluorouracyl, then the aromatase inhibitor is not aminogluthetimide.

## 19 AMENDED CLAIMS

[received by the International Bureau on 26 September 2000 (26.09.00); original claims 1, 2, 10 – 13 and 21 amended; remaining claims unchanged (4 pages)]

- 1. A composition for use in breast cancer therapy in humans comprising, in amounts effective to produce a superadditive antitumour effect, (a) an antineoplastic agent in a pharmaceutically acceptable carrier and/or diluent, and (b) an aromatase inhibitor in a pharmaceutically acceptable carrier and/or diluent, provided that the aromatase inhibitor is not aminogluthetimide.
- 2. A composition according to claim 1, wherein the antineoplastic agent is selected from an antineoplastic topoisomerase II inhibitor, an antineoplastic antimicrotubule agent, an antineoplastic alkylating agent, an antineoplastic antimetabolite and an antineoplastic topoisomerase I inhibitor, and the aromatase inhibitor is selected from exemestane, formestane, fadrozole, vorozole, letrozole, anastrozole and YM 511.

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- 3. A composition according to claim 2, wherein the antineoplastic agent is selected from an anthracycline compound, an anthraquinone compound, a podophillotoxine compound, a taxane compound, a vinca alkaloid, an alkylating agent, an antineoplastic antimetabolite agent and an antineoplastic topoisomerase I inhibitor.
- 4. A composition according to claim 3, wherein the anthracycline compound is selected from doxorubicin, epirubicin, idarubicin and nemorubicin; the anthraquinone compound is selected from mitoxantrone and losoxantrone, the podophillotoxine compound is selected from etoposide and teniposide; the taxane compound is selected from paclitaxel and docetaxel; the vinca alkaloid is selected from vinblastine and vinorelbine; the alkylating agent is selected from cyclophosphamide, ifosfamide, melphalan and PNU 159548; the antineoplastic antimetabolite agent is selected from 5-fluorouracil, capecitabine, gemcitabine, methotrexate and edatrexate, and the antineoplastic topoisomerase I inhibitor is selected from topotecan, irinotecan, 9-nitrocamptothecin and PNU 166148.
- 5. A composition according to claim 3, wherein such a composition comprises 1, 2 or 3 antineoplastic agents selected from epirubicin, doxorubicin, idarubicin, paclitaxel,

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about 1000 mg/m<sup>2</sup>;

- the effective antineoplastic amount of capecitabine is from about 10 mg/m<sup>2</sup> to about 1000 mg/m<sup>2</sup>;
- the effective antineoplastic amount of methotrexate is from about 10 mg/m<sup>2</sup> to about 1000 mg/m<sup>2</sup>;
- the effective antineoplastic amount of topotecan is from about 1 mg/m<sup>2</sup> to about 5 mg/m<sup>2</sup>;
- the effective antineoplastic amount of irinotecan is from about 50 mg/m<sup>2</sup> to about 350 mg/m<sup>2</sup>;
- and the effective amount of aromatase inhibitor is from about 0.5 to about 500 mg.
  - 8. A composition according to claim 7, wherein when administered orally, the amount of aromatase inhibitor exemestane is from about 5 to about 200 mg, fadrozole from about 0.5 to about 10 mg, letrozole from about 0.5 to about 10 mg, and anastrozole from about 0.5 to about 10 mg.
  - 9. A composition according to claim 7, wherein when administered parenterally, the amount of aromatase inhibitor exemestane is from about 50 to about 500 mg, and formestane is from about 250 to about 500 mg.
  - 10. A product containing an antineoplastic agent and an aromatase inhibitor, in amounts effective to produce a superadditive antitumor effect, for separate, simultaneous or sequential administration in breast cancer therapy in humans, and wherein the aromatase inhibitor is not aminogluthetimide.
  - 11. Use of an antineoplastic agent in the manufacture of a pharmaceutical composition for the treatment of breast cancer in a method additionally comprising the administration of an aromatase inhibitor, in amounts effective to produce a superadditive antitumor effect, and wherein the aromatase inhibitor is not aminogluthetimide.

12. A method for treating breast cancer in humans, the method comprising administering to a human in need thereof (a) an antineoplastic agent and (b) an aromatase inhibitor, in amounts effective to produce a superadditive antitumor effect, provided that the aromatase inhibitor is not aminogluthetimide.

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- 13. A method, according to claim 12, wherein the antineoplastic agent is selected from an antineoplastic topoisomerase II inhibitor, an antineoplastic antimicrotubule agent, an antineoplastic alkylating agent, an antineoplastic antimetabolite and an antineoplastic topoisomerase I inhibitor, and the aromatase inhibitor is selected from exemestane, formestane, fadrozole, vorozole, letrozole, anastrozole and YM 511.
- 14. A method according to claim 13, wherein the antineoplastic agent is selected from an anthracycline compound, an anthraquinone compound, a podophillotoxine compound, a taxane compound, a vinca alkaloid, an alkylating agent, an antineoplastic antimetabolite agent and an antineoplastic topoisomerase I inhibitor.
- 15. A method according to claim 14, wherein the anthracycline compound is selected from doxorubicin, epirubicin, idarubicin and nemorubicin; the anthraquinone compound is selected from mitoxantrone and losoxantrone; the podophillotoxine compound is selected from etoposide and teniposide; the taxane compound is selected from paclitaxel and docetaxel; the vinca alkaloid is selected from vinblastine and vinorelbine; the alkylating agent is selected from cyclophosphamide, ifosfamide, melphalan and PNU 159548; the antineoplastic antimetabolite agent is selected from 5-fluorouracil, capecitabine, gemcitabine, methotrexate and edatrexate, and the antineoplastic topoisomerase I inhibitor is selected from topotecan, irinotecan, 9-nitrocamptothecin and PNU 166148.
- 16. A method according to claim 14, wherein 1, 2 or 3 antineoplastic agents selected from epirubicin, doxorubicin, idarubicin, paclitaxel, docetaxel, 5-fluorouracil, cyclophosphamide and vinorelbine, and 1 or 2 steroidal aromatase inhibitors selected from exemestane, formestane, anastrozole, letrozole and fadrozole are administered.

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 $1000 \text{ mg/m}^2$ ;

- the effective antineoplastic amount of topotecan is from about 1 mg/m<sup>2</sup> to about 5 mg/m<sup>2</sup>;
- the effective antineoplastic amount of irinotecan is from about 50 mg/m<sup>2</sup> to about 350 mg/m<sup>2</sup>;

and the effective amount of aromatase inhibitor is from about 0.5 to about 500 mg.

- 19. A method according to claim 18, wherein when administered orally, the amount of aromatase inhibitor exemestane is from about 5 to about 200 mg, fadrozole from about 0.5 to about 10 mg, letrozole from about 0.5 to about 10 mg, and anastrozole from about 0.5 to about 10 mg.
- 20. A method according to claim 18, wherein when administered parenterally, the amount of aromatase inhibitor exemestane is from about 5 to about 500 mg, and formestane is from about 250 to about 500 mg.
- 21. A method for lowering the side effects in humans caused by breast cancer therapy with an antineoplastic agent, the method comprising administering to a human in need thereof a combined preparation comprising (a) an antineoplastic agent and (b) an aromatase inhibitor, in a quantity to produce a superadditive antitumor effect, provided that the aromatase inhibitor is not aminogluthetimide.